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FDG PET in oral and oropharyngeal cancer. Value for confirmation of N0 neck and detection of occult metastases

Christiaan A. Krabbe ^{a,*}, Pieter U. Dijkstra ^{a,b}, Jan Pruim ^c,
Bernard F.M. van der Laan ^d, Jacqueline E. van der Wal ^e,
Joost P. Gravendeel ^f, Jan L.N. Roodenburg ^a

^a Department of Maxillofacial Surgery, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

^b Center for Rehabilitation, University Medical Center Groningen, Groningen, The Netherlands

^c Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, Groningen, The Netherlands

^d Department Otorhinolaryngology, University Medical Center Groningen, Groningen, The Netherlands

^e Department of Pathology, University Medical Center Groningen, Groningen, The Netherlands

^f Department of Radiology, University Medical Center Groningen, Groningen, The Netherlands

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Summary Treatment of the clinical N0 neck in squamous cell carcinoma (SCC) of oral cavity and oropharynx remains a dilemma. None of the current imaging modalities are able to detect the presence of micrometastases in the lymph nodes of clinical N0 necks reliably. The aim of this study was to determine the diagnostic properties of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) in patients clinically staged as N0. FDG PET results of 38 patients were compared to histologic specimens obtained with neck dissections or to follow-up. FDG PET performance was compared to computed tomography (CT), magnetic resonance imaging (MRI) or ultrasonography-guided fine needle aspiration cytology (USgFNAC). Sensitivity and specificity of FDG PET in detecting occult cervical metastases were 50% and 97% respectively. Although FDG PET performed better than conventional imaging modalities, sensitivity was lower than desired. As a consequence, clinical application of FDG PET in the patient staged as N0 is limited.

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* Corresponding author. Tel.: +31 50 3612567; fax: +31 50 3611136.
E-mail address: c.a.krabbe@kchir.umcg.nl (C.A. Krabbe).

Introduction

The presence of cervical lymph node metastases at the time of diagnosis of squamous cell carcinoma (SCC) of the upper aerodigestive tract has a great impact on patient's treatment and prognosis.^{1,2} In planning treatment, staging of the neck is essential. It is important to distinguish between a N0 and a N+ neck. The common diagnostic procedures for cervical lymph node staging are clinical examination, computer tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) with ultrasound-guided fine-needle aspiration cytology (USgFNAC) on indication. Unfortunately a diagnosed N0-neck is still at risk of harboring occult cervical lymph node metastases. Prevalences of occult spread range from 12% to 50%, basically depending on the location and the size of the primary tumor.^{3–5} Although CT and MRI of the neck have proven to be superior to palpation in detecting cervical metastases, these modalities still have low accuracy for confirming the N0-neck. Between 40% and 60% of all occult metastases are found using either CT or MRI at the cost of a relatively high rate of false positives.⁶ In contrast, USgFNAC has a higher sensitivity and specificity and is more cost-effective than CT and MRI. In experienced hands, the sensitivity for the N0 neck can reach 73% with a specificity of 100%,⁷ although others reported sensitivities ranging from 42% to 50%.^{8,9}

Because of the risk of occult cervical metastases in a diagnosed N0-neck in oral and oropharyngeal SCC the best treatment still is a dilemma. In cases of a N0 neck with a low risk for occult metastases watchful waiting is acceptable. However, if there is a high risk for occult cervical metastases an elective neck dissection is usually performed. A generally accepted maximal risk for subclinical disease in which case a watchful waiting policy is followed is 20%.¹⁰

In recent years positron emission tomography (PET) with 2-(F18)-fluoro-2-deoxy-D-glucose (FDG) has become an additional tool in the staging of head and neck cancer. In comparison with CT and MRI, FDG PET seems to be the procedure with the highest sensitivity and specificity for detecting lymph node metastases of head and neck cancer.¹¹

Aim of this study was to determine the diagnostic properties of FDG PET in patients clinically staged as N0 compared to routine work-up consisting of MRI, CT and USgFNAC.

Materials and methods

All patients with a newly diagnosed SCC of the oral cavity or oropharynx without signs of cervical lymph node metastasis in the physical examination (clinical N0-neck) who underwent FDG PET scanning from December 1999 till December 2003 were selected from medical records ($n = 44$). The PET scan was acquired for staging purposes before onset of treatment. Squamous cell carcinoma was histologically confirmed before patients were referred for FDG PET scanning. Five patients without neck dissection who underwent elective radiation therapy of the neck were excluded for they could not be evaluated reliably during follow-up because of the previous neck treatment. Another patient was excluded because of loss of the FDG PET results. In total 38 patients were included.

Patients were referred for whole body FDG PET by the Departments of Maxillofacial Surgery and Oto-Rhino-Laryngology. The scans were acquired on two cameras: a Siemens CTI ECAT 951 (31 planes over 11.8 cm) and a Siemens CTI ECAT EXACT HR + (63 planes over 15.5 cm). The resolutions of the systems are 6 mm full width at half maximum transversally in the center of the field of view, and 5 mm respectively. The patients fasted for at least 4 h before receiving the intravenous administration of FDG. Each patient received five megabecquerel of FDG per kilogram. The time interval between intravenous FDG injection and PET-imaging was 90 min. An experienced nuclear medicine physician interpreted the scan results by visual evaluation. Standard uptake value (SUV) calculations were not performed. Besides staging the neck, the FDG PET whole body scan was also evaluated in detecting distant metastases or second primary tumors. At the time of FDG PET imaging no patient had clinical evidence of distant metastases or second primary tumors.

Next to FDG PET each patient underwent conventional imaging consisting of CT ($n = 19$), MRI ($n = 10$) or US with fine needle aspiration cytology ($n = 5$) or US without ($n = 4$) fine needle aspiration cytology.

The results of FDG PET and the conventional imaging modalities were obtained by studying the radiological and nuclear medicine reports. The FDG PET and conventional imaging modality results were compared to the histology of the neck specimens obtained during neck dissection. Histopathological examination of the lymph nodes was performed on hematoxylin-eosin stained slides. The lymph node was cut in one or more slices, depending on the size of the lymph node, and completely embedded. If no neck dissection was performed, the results were compared to the results of clinical follow-up with a minimum of 1.5 years.

Sensitivity, specificity, accuracy, positive predictive value and negative predictive value of FDG PET and the conventional imaging modalities were calculated.

Results

Primary tumor

The study group consisted of 38 patients, 17 females and 21 males with a median age of 59 (IQR 53, 68) years. Tumor stage and localization are shown in Table 1.

FDG PET did detect the squamous cell carcinoma at the primary site in 36 patients (sensitivity of 95%). The two tumors not detected by FDG PET were superficial T1 tumors localized in the floor of the mouth.

Table 1 Localization and pathological stage of the 38 tumors

	T1	T2	T3	T4
Oral tongue	7	6	3	
Gum	2		1	4
Floor of mouth	6	1		3
Base of tongue		2		
Tonsillar fossa		2	1	

The neck

In 30 patients a neck dissection was performed with a median of 8 (IQR 2, 20) days after the PET study. The eight patients without neck dissection had a median follow-up of 3.8 (IQR 1.7, 4.1) years. There was evidence of a positive neck on histology in seven patients and by follow-up in one patient. The prevalence of occult cervical metastases was 21% (8/38) in this study-population. FDG PET detected cervical metastases in five patients. Four of these five scans were true positive, one was false positive. PET scans were negative for cervical metastases in 33 patients, 29 of them showed indeed no evidence of disease by histology or follow-up. In the other four patients, all in the dissection group, FDG PET was false negative (Table 2). The cervical metastases detected by FDG PET varied in size from 4 to 7 mm. The sizes of the non-detected cervical metastases were respectively 1 mm, 7 mm, 9 mm and 15 mm.

Because FDG PET recognized four of the eight patients with occult cervical metastases the prevalence of occult cervical metastases in this study decreased from 21% to 11% (4/38). As patients with a T1 tumor are often subjected to a watchful waiting protocol, while patients with a T2 or higher tumor stage are subjected to elective treatment of the neck, the impact of FDG PET on prevalence of occult cervical metastases of these two groups was assessed. The results revealed that in T1 ($n = 15$) and T2–T4 patients ($n = 23$) the prevalence of occult cervical metastases decreased from 13% (2/15) to 7% (1/15) and from 26% (6/23) to 13% (3/23), respectively.

The diagnostic properties of the conventional imaging methods are presented in Table 2. Table 3 shows the results of each conventional imaging technique separately. CT ($n = 19$) detected one occult cervical metastasis more with six more false positive results comparing to FDG PET. MRI ($n = 10$) detection rate was identical to FDG PET but MRI showed two more false positive results. In the group of US(gFNAC) ($n = 9$) the one patient with an occult cervical metastasis was only detected by FDG PET, US(gFNAC) showed no false positive results.

Distant metastases and second primary tumors

In this patient population no distant metastases were seen. In three patients a second primary tumor was found. FDG

Table 3 Results of conventional imaging techniques in diagnosing occult cervical metastases compared with FDG PET for each modality separately

	Occult cervical metastases		
	Present	Absent	Total
CT ($n = 19$)			
CT+	2	7	9
CT–	1	9	10
Total	3	16	19
FDG PET+	1	1	2
FDG PET–	2	15	17
Total	3	16	19
MRI ($n = 10$)			
MRI+	2	2	4
MRI–	2	4	6
Total	4	6	10
FDG PET+	2	0	2
FDG PET–	2	6	8
Total	4	6	10
US(gFNAC) ($n = 9$)			
US(gFNAC)+	0	0	0
US(gFNAC)–	1	8	9
Total	1	8	9
FDG PET+	1	0	1
FDG PET–	0	8	8
Total	1	8	9

CT – computed tomography, MRI – magnetic resonance imaging, US(gFNAC) – ultrasound(-guided fine-needle aspiration cytology), FDG PET – fluorine-18 fluorodeoxyglucose positron emission tomography.

PET discovered two of these exclusively: an esophageal carcinoma and a bronchial carcinoma. Due to this detection, these two patients could receive treatment with curative intent. The third patient had a superficial T1 second primary tumor of the tongue, which was discovered by examination under general anesthesia. Three times FDG PET was false positive for a second primary tumor or distant metastases.

Table 2 Diagnostic value of FDG PET and the conventional imaging methods in the detection of occult cervical metastases in the N0-neck in SCC of the oral cavity and oropharynx

	Occult cervical metastases			
	Present	Absent	Total	
FDG PET+	4	1	5	Sensitivity 50% (CI: 21.5–78.5); PPV 80% (CI: 37.6–96.4) Specificity 97% (CI: 83.3–99.4); NPV 88% (CI: 72.7–95.2) Accuracy 87% (CI: 0.73–0.94); LR 15 (CI: 2.5–91.3)
FDG PET–	4	29	33	
Total	8	30	38	
Conventional+	4	9	13	Sensitivity 50% (CI: 21.5–78.5); PPV 31% (CI: 12.7–57.6) Specificity 70% (CI: 52.1–83.3); NPV 84% (CI: 56.4–93.6) Accuracy 66% (CI: 0.50–0.79); LR 1.7 (CI: 0.6–3.7)
Conventional–	4	21	25	
Total	8	30	38	

Total population $n = 38$. FDG PET – fluorine-18 fluorodeoxyglucose positron emission tomography, conventional – conventional imaging methods consisting of computed tomography, magnetic resonance imaging or ultrasound-guided fine-needle aspiration cytology, PPV – positive predictive value, NPV – negative predictive value, LR – positive likelihood ratio, CI – 95% confidence interval.

Discussion

Despite advances in imaging technology, none of the current imaging modalities is able to detect the presence of micrometastases in the lymph nodes of clinical N0 necks reliably. In the current study FDG PET and conventional imaging methods separately detected four of the eight patients with occult cervical metastases. Two patients were detected by both FDG PET and conventional imaging methods. Of the four metastases that were not detected by FDG PET one metastasis had a diameter of 1 mm which is far beyond the resolution of FDG PET. The 7 mm and 9 mm cervical metastases were probably not detected because of a high blood sugar level (7.7 mm/L) and high FDG uptake by the muscles in the neck region, respectively, factors that lower the contrast ratio between tumor and background. The undetected cervical metastasis of 15 mm was in clinical setting confused with nonspecific activity of the parotid gland, though by reviewing clearly outlined as a hotspot indicating metastasis.

FDG PET has a higher specificity, positive and negative predictive value and accuracy in comparison to the conventional methods (Table 2). The difference is predominantly determined by one false-positive result by FDG PET and nine false positive results by the conventional methods (CT and MRI). Although there is no difference in sensitivity for both techniques, the positive likelihood ratio differs considerably: 15 for FDG PET and for the conventional methods 1.7. Because of the lower positive likelihood ratio the conventional imaging methods could lead to higher numbers of overtreatment compared with patients who were diagnosed by FDG PET.

The accuracy of CT and MRI for nodal assessment is to a great extent restricted by the criteria used for lymph node metastasis. Criteria which result in a higher sensitivity subsequently will lead to a lower specificity and vice versa. While CT and MRI detect changes of morphology, structure and of diameter, FDG PET reveals the changes in cell metabolism and therefore is not dependent on criteria used.

USgFNAC performed better than CT and MRI in specificity, because it is very unlikely to have a false positive result. There was only one false negative result of USgFNAC, which was detected by FDG PET. This false negative result is in accordance with the finding that approximately 20% of the patients with negative USgFNAC at the time of presentation developed a neck node metastasis during follow-up.¹²

In most studies in which FDG PET is compared to the conventional imaging modalities FDG PET seems to be superior for accurate staging of the neck.^{11,13} The role of FDG PET in patients staged as N0 is less clear. In two studies FDG PET performed better than conventional imaging techniques in the N0 neck.^{14,15} One study found a better performance by the conventional imaging methods probably because of simultaneous use of more than one conventional imaging modality in most patients which resulted in a higher overall sensitivity.¹⁶

Because of the risk of occult metastases, the treatment of the clinical N0-neck in squamous cell carcinoma of the head and neck remains controversial. A generally accepted concept is to apply a watchful waiting when the risk of occult cervical metastases is estimated to be 20% or less.¹⁰ In

this study the addition of FDG PET to clinical investigation reduced the risk of occult cervical metastases in the clinical negative neck from 21% to 11%. The negative predictive value of FDG PET was 88% which implies that a patient with a negative PET scan has a risk of occult metastases below the threshold of 20%. In practice, the threshold of 20% would imply that most patients with tumors staged as T2 or larger should undergo some form of elective treatment, inevitably leading to excess treatment in most patients. In this study the prevalence of occult metastases was 26% in the T2–T4 group. As shown, FDG PET decreased the risk of occult metastases in the T2–T4 group to 13%. The negative predictive value was 84%. Three other studies also found a negative predictive value above 80%.^{14,16,17} This could suggest that this T2–T4 group might be suitable for a watchful waiting policy in case of a negative PET scan. However, due to the low prevalence of cervical metastases in this population a relatively high number of true negative results is expected which will result in a higher specificity and negative predictive value. As a consequence, because of this possible bias, it is yet not appropriate to conclude that a negative FDG PET scan could be suitable for watchful waiting policy in the N0 neck.

Only a limited number of FDG PET studies in head and neck cancer patients with a clinically negative neck have been reported.^{14–22} These studies show different sensitivities for the detection of occult cervical metastases by FDG PET ranging from 0% to 100% (Fig. 1). The specificities in these studies differ in a less broad range: 76–100%. We found a specificity of 97% due to one false-positive result.

The broad range in sensitivities found in the above mentioned studies can be explained by the use of different research methods such as sample size, definition of N0-neck, gold standard, and administration of FDG.

Overall the study samples were small (range $n = 11–31$) which leads to broad confidence intervals.

The most important inclusion criterion used in all studies is the clinically negative neck. This is not a clearly defined term.²³ In this study as well as in three other studies,^{14–16} the N0 neck was determined by physical examination (palpation) only. In the other five studies the clinically negative neck was defined by both physical examination and radiological investigation.^{17–21} The two different definitions of a N0-neck used by these studies resulted in high and low sensitivities respectively, with the exception of the FDG PET/CT study.¹⁷ In the current study the sensitivity would have dropped from 50% to 33% if the results of CT scanning had been used in the definition of a clinically N0-neck.

The histopathological examinations of neck dissections in all mentioned studies are used as the gold standard for comparison with FDG PET results. Different histopathological methods may cause different sensitivities. If the lymph nodes of a neck dissection are examined in more detail, more occult metastases are found.^{3,24–26} Studies in which lower sensitivities were found^{18–20} used step sectioning and immunohistochemistry as part of histopathological work-up.

Other factors to influence the sensitivity are the PET camera used and the means of administration of FDG. The PET cameras used in the above mentioned studies are different in brand, type and resolution. The time interval between intravenous FDG injection and PET imaging

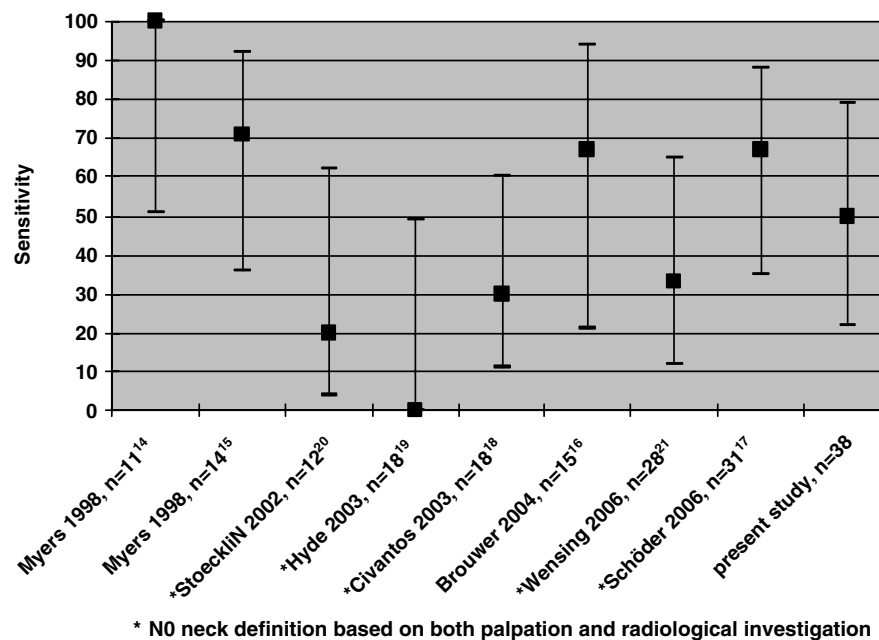


Figure 1 Sensitivity of FDG PET with CI 95% in detecting occult cervical metastases in the N0-neck in different studies.

coincides with the uptake of FDG by tumor. Delineation of metastases from normal tissue background is important. A greater time interval improves image contrast and thus tumor detectability.^{27–29} An uptake period of 90 min is appropriate for performing clinical static PET imaging of primary head and neck cancer.^{30,31} Especially in detecting micrometastases the tumor-to-background ratio is important. In the studies mentioned above PET acquisition was about 60 min or less after intravenous injection of FDG and this may not be enough to detect occult metastases adequately.

Considering all the differences in study methods it is not surprising that sensitivities differ in a broad range. Camera development and the use of other tracers than FDG might improve the diagnostic properties of PET in the N0 neck. Because of combining two modalities FDG PET/CT might find higher sensitivities.

From this study, it is concluded that, although FDG PET seems to have the best accuracy for detecting occult cervical metastases in the clinical N0 neck in SCC of the oral cavity and oropharynx when compared to other imaging techniques, the sensitivity is still lower than desired.

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